

Application No.: 10/031,695
Inventor: HAUER et al.
Reply to Office Actions of 30 November 2005
26 April 2006 & 20 June 2006
Docket No.: 51241

REMARKS/ARGUMENTS:

Claims 1-12, 14 and 16-18 are currently pending. Claims 12, 14 and 17-18 are amended.

Rejection under 35 USC §112 ¶2

Claim 12 stands rejected as allegedly indefinite. Applicants respectfully traverse this rejection and incorporate all remarks made in Applicants' prior USPTO communications.

Determining whether a claim is definite requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more (*Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875, (Fed. Cir. 1993)).

The Examiner states that the phrases "isolating resulting hydroxylated product from the medium" and "subterminally hydroxylated aliphatic carboxylic acids" are unclear. Applicants respectfully disagree. The Examiner asserts that it is material whether or not terminally hydroxylated products are obtained. Applicants claimed invention provides a method for hydroxylating an aliphatic C₈-C₁₂-carboxylic acid. The degree of purity of the obtained product is irrelevant as long as the instant claimed invention meets the requirements for patentability. The instant invention solves the technical problem of providing a process for production of subterminally hydroxylated carboxylic acids. No essential steps are omitted and those of ordinary skill are fully and completely able to practice this method from a reading of the claims in light of the Specification.

The Examiner supports the stated opinion with the argument that "it is not clear how subterminally hydroxylated carboxylic acids are separated from terminally hydroxylated carboxylic acids." Applicants respectfully disagree. Recently, the Federal Circuit stated in *Capon v. Eshhar*, that an application must be reviewed in accordance with the relevant skill in the art at the time of filing and as the skill advances, so must the review (418 F.3d 1349 (Fed.

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Cir. 2005)). Applicants respectfully submit that at the time of filing, isolation of subterminally hydroxylated product would have been a routine skill for one of ordinary skill in the art. Further, Method 6 on page 18 of the instant Specification discloses chromatographic methods. More specifically, Method 6 b) teaches analysis by gas chromatography. Consequently, the phrases "isolating resulting hydroxylated product from the medium" and "subterminally hydroxylated aliphatic carboxylic acids" are clear and Applicants respectfully request withdrawal of the instant 112 rejection.

Claim 14 stands rejected as indefinite. The Examiner asserts that it is unclear if the amino acid substitutions are in the alternative or are all inclusive. While neither agreeing with the Examiner's reasons for said objection nor with said rejection's correctness, Applicants amended the claims to make clear the grouping of the substitutions referred to by the Examiner in order for a more timely prosecution of the instant application. Applicants thusly request withdrawal of the instant 112 rejection.

Claims 12, 14 and 16-18 stand rejected as indefinite for allegedly failing to point out and distinctly claim the subject matter which the Applicants regards as the invention. The Examiner asserts that the metes and bounds of the phrase "is derived from *Bacillus megaterium*" are unclear. Applicants respectfully disagree. While the Examiner provides a number of entertaining dictionary variations on possible meanings of the term "derived," Applicants urge that one of ordinary skill in the art, the practitioner against whom all §112 ¶2 rejection for indefiniteness are based, would readily understand the meaning of said term in the context of the instant application. The Examiner is reminded that it is well settled that the "language of the claims, read in light of the specification" is to be considered when determining whether the claims are definite (*Allen Archery Inc. v Browning MFG. Co.*, 819 F.2d 1087, 1092 (Fed. Cir. 1987)). This precept has been incorporated into the MPEP which states that "[t]he meaning of every term used in any of the claims should be apparent from the descriptive portion of the specification with clear disclosure as to its import." (MPEP §608.01(o). See also 37 CFR 1.75 (c) wherein it states in part that "the meaning of the terms in the claims may be ascertainable by reference to the description.")

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Moreover, the definiteness of the language employed "must be analyzed - not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one processing ordinary skill in the pertinent art" (*In re Angstadt*, 537 F.2d 498, 501 (CCPA 1976)(quoting *In re Moore*, 439 F.2d 1232, 1235 (CCPA 1971)). The law is clear that "if the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more" (*North Am. Vaccine, Inc. v American Cyanamid Co.*, 7 F.3d 1571, 1579-1580 (Fed. Cir. 1993)).

Applicants direct the Examiner to the paragraph bridging pages 2 and 3 of the instant Specification, wherein Applicants explain what is done when a monooxygenase is derived from *B. megaterium*.

The Examiner's interpretation of Applicants' claims clearly fails to meet the standards set by the Court that "claims yet unpatented are to be given the broadest reasonable interpretation consistent with the specification" (See, *In re Prater and Wei*, 162 USPQ 541, 550 (CCPA 1969)). The Examiner's interpretation of Applicants' claims is neither reasonable nor consistent with the specification. Accordingly, Applicants assert the metes and bounds of the phrase "is derived from *Bacillus megaterium*" are clear to one of ordinary skill in the art when said claim term is read in light of the instant Specification.

Claims 12, 14 and 16-18 stand rejected as indefinite for allegedly failing to point out and distinctly claim the subject matter which the Applicants regards as the invention. The Examiner asserts that the metes and bounds of the terms "in accordance with SEQ ID NO:2" and "according to SEQ ID NO:2" are unclear. While neither agreeing with the Examiner's reasons for said objection nor with said rejection's correctness, Applicants amended the claims referred to by the Examiner in order for a more timely prosecution of the instant application. In claim 12, the phrase "in accordance with" has been deleted and replaced with the term "containing," and in claim 14, the phrase "according to" has been deleted and replaced with the term "of." In light of the aforementioned amendments, Applicants respectfully request withdrawal of the instant 112 rejection.

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Claims 12, 14 and 16-18 stand rejected as indefinite for allegedly failing to point out and distinctly claim the subject matter which the Applicants regards as the invention. The Examiner asserts the metes and bounds of the term "functional mutation" are unclear. Applicants respectfully disagree. Similar to the above arguments, the claims must be analyzed in light of the Specification and are to be given the broadest reasonable interpretation consistent with the Specification. In this regard, the Examiner is directed to page 3, lines 13-17 of the instant Specification for a reading of the term "functional mutation" which states:

A "functional mutation" for the purposes of the present invention encompasses an amino acid exchange in the abovementioned sequence regions which results in an "altered reactivity pattern" or "altered substrate profile" in accordance with the above definition.

Thus, Applicants respectfully assert that a "functional mutation" is one that provides an alteration of the reactivity pattern and/or substrate profile as compared with wild type P450 monooxygenase as would be readily apparent and determinable by one of ordinary skill in the art. Accordingly, because all of the Examiner's rejection under 35 USC §112 ¶2 have been addressed and overcome, Applicants respectfully request withdrawal of said rejection. Favorable action is solicited.

Rejection under 35 USC §112 ¶1

Claims 12, 14 and 16-18 stand rejected for allegedly failing to convey to one skilled in that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree.

In regards to all the 112 ¶1 rejection, it must be remembered that to satisfy the written description prong of 35 USC §112 ¶1, the Specification must only describe the invention in sufficient detail so that one skilled in the art can clearly conclude that "the inventor invented the claimed invention" (*Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)). No particular form of disclosure is required, but "the description must clearly allow persons of ordinary skill in the art to recognize that [the patentee] invented what is claimed" (*In re Gosteli*,

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872 F.2d 1008, 1012 (Fed. Cir. 1989)) (citing *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976)).

The Examiner believes that the limitation that a derivative of C₈-C₁₂-carboxylic acids be selected from an alkyl ester, an amide or an anhydride thereof and the limitation that if the mutant enzyme comprises F87A, said mutant must comprise another mutation is not described in the instant Specification as filed. Applicants respectfully disagree.

The Examiner is directed to part a1) of claim 12, as originally filed, wherein said claim recites a recombinant microorganism as claimed in claim 10 or 11. Claim 10 in turn refers to a vector according to claim 9, comprising an expression construct according to claim 8, which encodes a nucleic acid sequence as claimed in claim 7. Said nucleic acid encodes a monooxygenase as claimed in any of the preceding claims, and consequently, encodes a monooxygenase according to claim 3. Claim 3 recites the aforementioned rejected limitation. Further, part a2) of claim 12, as originally filed, directly refers to a monooxygenase of any of claims 1 to 6, and as such, also to a monooxygenase according to claim 3.

Further still, the Examiner is directed to the instant Specification, page 10, lines 33-38, wherein C₈-C₁₂-carboxylic acids and their derivatives are disclosed as especially preferred embodiments of the instant invention. Applicants respectfully assert that a skilled artisan would have been aware of alkyl esters, amides and anhydrides as potential derivatives, especially since said derivatives, in addition to being known in the art, have been disclosed on page 2, lines 35-36 of the instant Specification. Accordingly, the instant Application, as filed, supports the rejected claims.

Indeed, the claims are written in such a manner that the problems of insufficient numbers of examples as described by the Examiner in the Office Action should not apply. The MPEP states that a "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces" and as such, a single species may be enough to identify the entire genus (*see* MPEP 2163.II.A.3.a.ii.). With respect to the written description requirement, the Federal Circuit stated: "[t]he 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the

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balance also evolves between what is known and what is added by each inventive contribution" (*Capon v. Eshhar* at 1358). Further, in overturning a BPAI decision, which relied on similar rejection reasons as stated in the instant Office Action, where both parties to an interference had all claims in their respective patents cancelled for failing to meet the written description requirement, the court stated that "[t]he Board erred in refusing to consider the state of the art of the scientific knowledge" and when citing *Lilly* and *Fiers* spoke of a rulings in view of a "wish" list provided in said inventions, and not the state of the relevant art (*Id.* at 1357). Further, the court stated, that "[i]t is not necessary that every permutation with a generally operable invention be effective in order for an inventor to obtain a generic claim" and both parties were landed because they "present[ed] not only general teachings... but also specific examples" (*Id.* at 1359).

Applicants respectfully assert that the instant Specification complies with all the aforementioned requirements because it allows one of ordinary skill in the art to practice the instant invention. Applicants provide in the instant Specification summary information such as the function of cytochrome P450 monooxygenase and general molecular biology techniques which meet the "general teachings" prong. Further, Applicants supplied "specific examples" of the instant invention as part of the second prong of *Capon*. As the listed by the Examiner on page 8 of the 30 November 2005 Office Action, the instant Specification teaches a method for hydroxylating 15-pNCA, 12-pNCA, 10-pNCA or 8-pNCA with a modified P405 monooxygenases of SEQ ID NO:2 having mutations at residue 26, 47, 74, 87, 188 or 354. Thus, while not required to provide even a single working example (*See, In re Gosteli* above - no specific form of the disclosure is required), Applicants provided such examples as set forth above.

The Examiner, in stating on page 8 of the 30 November 2005 Office Action that the "limited examples are not enough" to claim a genus, has erroneously mandated a quantifiable number of examples. Any requirement for a mandatory number of examples is contrary to USPTO practice and as such, the Examiner's statement indicating an insufficiency in the number of examples disclosed in the instant specification is in error. If however, contrary to Applicants assertions above, the Examiner has personal information not of record used to determine

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"sufficient" numbers of examples, Applicants respectfully request an Examiner's affidavit indicating the use of personal knowledge and allowance for Applicants to respond to said personal knowledge.

In this regard, Applicants disclosed a sequence to be used as the basis for mutations, SEQ ID NO:2, selected regions to be mutated in order to obtain a desired effect and the mutants themselves. The Examiner is directed again to MPEP 2163.II.A.3.a.ii., wherein it states, when describing the disclosed species requirements for a claimed genus, that "a "representative number" [of species] is an inverse function of the skill and knowledge in the art." Further application of *Capon* is required here because the skill and knowledge in the field at the time of filing was such that the examples disclosed in the instant specification provide sufficient description of a representative number of species by actual reduction to practice. Consequently, the instant invention has been sufficiently disclosed and sufficiently supported by experimental data wherein sufficient written description for the entire genus based on the applicable standards is provided. Therefore, Applicants respectfully assert that the Examiner has applied too strict an interpretation for claiming a genus and that Applicants are entitled to claim additional embodiments which are not represented by individual examples, i.e. the genus from the species recited.

Accordingly, for at least the reasons described above, the instant Application provides an adequate written description for one of ordinary skill in the art to practice the instant invention and withdrawal of the instant rejection is respectfully requested. The instant Specification, in combination with what would have been known by a skilled artisan at the time of filing, provides sufficient written description support to clearly conclude that the inventor "at the time the application was filed, had possession of the claimed invention."

Regarding the enablement requirement of §112, the Federal Circuit has held that "[t]he specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation'." (*Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. (2003))). Applicants

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respectfully assert that the claims, as currently amended, are fully enabled by the Specification of the instant application in combination with the general knowledge of one of ordinary skill in the art.

The Examiner recited the standard USPTO phraseology in rejecting the instant claims. Applicants respectfully assert that said phraseology is inappropriate for the instant application. The Examiner alleges, for example, that the instant disclosure presents no guidance or working examples of the use of any or all mutants, recombinants, or variants of any or all cytochrome P450 monooxygenase. Applicants respectfully disagree and direct the Examiner to the instant claims wherein it is recited that said invention relates to a nucleic acid sequence encoding a monooxygenase which is derived from *Bacillus megaterium* cytochrome P450 monooxygenase BM-3 with an amino acid sequence of SEQ ID NO:2 which has a functional mutation in the amino acid sequence region 86-88. The claims, contrary to the Examiner's assertions, allow one of ordinary skill to practice the instant invention without undue experimentation. As stated above, the instant Specification provides a number of working examples for the skilled artisan to use as a basis for the practice of the instant invention. Additionally, as described in *Capon*, as the skill in the art progresses so to does the analysis of the inventions in said art. Applying *Capon* and the relative state of the art at the time of filing, one of ordinary skill would be able to create the working examples the Examiner asserts are lacking.

Further, instant claims 14 and 18 indicate specific individual amino acid mutations. Applicants respectfully assert that the amount of direction and guidance provided by showing these mutation sites would have enabled one of ordinary skill to practice the instant claimed invention.

Further still, the Examiner asserts that the specific amino acid positions within a given protein sequence that can be modified is unpredictable and that one of skill in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification. Applicants respectfully disagree. The Examiner is directed to MPEP 2164.04 which states in regards to an enablement rejection, quoting *In re Marzocchi*, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it

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doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement" (439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)). The Examiner has provided no evidence to support the above statement that the skilled artisan would expect any tolerance to diminish. If, contrary to Applicants assertions that the instant invention is enabled, the Examiner has used information from examples not of record, Applicants respectfully request an Examiner's affidavit indicating the use of personal knowledge and allowance for Applicants to respond to said personal knowledge.

Moreover, computational techniques were available at the time of filing for protein structural predictions based on sequence listings. The Examiner is directed to, for example, the Boston University Protein Sequence Analysis server (available at <http://bmerc-www.bu.edu/psa/>), which has been available since at least the filing date of this application. Consequently, modification of the instant claimed sequence in regards to the instant claims, would have been routine to one of ordinary skill in the art.

Additionally, The Examiner has provided no evidence to support the assertions of undue experimentation. The Examiner, in the 30 November 2005 Office Action states at least the following:

1. "It would require undue experimentation of the skilled artisan to hydroxylate any carboxylic acid." Page 11
2. "It would require undue experimentation of the skilled artisan to make and use the claimed variants and mutants." Page 12
3. "[T]he claimed invention would require undue experimentation." Page 12

Applicants respectfully disagree. In order to establish a *prima facie* rejection, the Examiner must provide evidence of the necessity of said "undue experimentation." Along these lines, the Examiner has not stated why one skilled in the art could not supply the allegedly needed enabling information without undue experimentation. If the Examiner has personal knowledge regarding experimentation volume, Applicants respectfully request submission of an Examiner's affidavit and the opportunity to respond. In the absence of such evidence or an

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affidavit, Applicants respectfully request that this rejection be withdrawn.

In sum, Applicants respectfully assert that the instant claims are enabled based upon the requirements of §112, the MPEP and the rulings handed down from the Federal Circuit. One of ordinary skill in the art would have been able to practice the instant invention without undue experimentation based on a combination of the contents of the instant Specification when analyzed by the skill in the art at the time of filing. Accordingly, Applicants respectfully request withdrawal of the instant enablement rejection and favorable action is solicited.

Rejection under 35 USC §102

Claims 12, 14 and 16-18 stand rejected as allegedly anticipated by Graham-Lorence et al. Applicants respectfully disagree.

Anticipation can only be established by a single prior art reference which discloses each and every element of the claimed invention (*RCA Corp. v. Applied Digital Data Systems, Inc.*, 730 F.2d 1440, 1444 (Fed. Cir. 1984)). The identical invention must be shown in as complete detail as it is contained in the ... claim" (*Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)). It is not enough, however, that the reference discloses all the claimed elements in isolation. Rather, as stated by the Federal Circuit, the cited art reference must disclose each element of the claimed invention "arranged as in the claim" (*Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)).

Amended claim 12 recites at least one hydroxylatable C₈-C₁₂-carboxylic acid or a derivative of C₈-C₁₂-carboxylic acid. As discussed above, the claims must be read in light of the Specification, they must not be read in a vacuum. Applicants respectfully urge that reading the term C₈-C₁₂-carboxylic acid or a derivative of C₈-C₁₂-carboxylic acid to read on a 20 carbon fatty acid is reading said claim recitation in a vacuum and devoid of the disclosure of the instant Specification. As a result, the cited art fails to teach, suggest or disclose an element, a C₈-C₁₂-carboxylic acid or a derivative of a C₈-C₁₂-carboxylic acid, of instant claim 12 and as such, fails to anticipate said claim.

For at least the arguments listed above, Graham-Lorence et al. fails to teach, suggest or

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disclose each and every element of the instant claims as arranged in said claims. Because the cited art does not teach each and every element of the claims, it does not anticipate the claims.

Applicants therefore respectfully request withdrawal of the rejection under 35 USC § 102(b).

Favorable action is solicited.

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Conclusion

Applicants respectfully submit that the present application is in condition for allowance, which action is courteously requested. Please charge any shortage in fees due in connection with the filing of this paper to Deposit Account 14.1437. Please credit any excess fees to such account.

Respectfully submitted,



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